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Amide α,β-Dehydrogenation Using Allyl-Palladium Catalysis and a Hindered Monodentate Anilide

Yifeng Chen, Aneta Turlik, and Timothy R. Newhouse*

Department of Chemistry, Yale University, 275 Prospect Street, New Haven, Connecticut 06520-8107, United States

Supporting Information

ABSTRACT: A practical and direct method for the α,β-dehydrogenation of amides is reported using allyl-palladium catalysis. Critical to the success of this process was the synthesis and application of a novel lithium *N*-cyclohexyl anilide (LiCyan). The reaction conditions tolerate a wide variety of substrates, including those with acidic heteroatom nucleophiles.

A greater number of modes of reactivity become available by increasing the oxidation state of organic compounds through dehydrogenation. Dehydrogenation methodologies for the conversion of alcohols to ketones, amines to imines, and alkanes to alkenes can be made more sustainable through the development of transition metal catalyzed reactions.[1] Palladium complexes have emerged as the most practical metal catalysts for the introduction of alkenes adjacent to carbonyls,[2,3] including α,β-dehydrogenation via the enoxysilane by the two-step Saegusa oxidation.[3d] Stahl and co-workers obviated the requirement for the synthesis of the enoxysilane by developing a method that oxidizes ketones and aldehydes directly by a C−H insertion mechanism.[3f,g] Recently we reported conditions for α,β-dehydrogenation of the more electron-deficient and less acidic esters and nitriles using allyl-palladium catalysis (Figure 1a).[4]

Despite the prevalence of amides in proteins,[5] bioactive molecules,[6] and polymers,[7] a general and direct method for amide α,β-dehydrogenation has not been developed.[8−10] A commonly employed strategy relies on the Sharpless process, which requires α-selenation followed by a second oxidation step wherein selenoxide elimination occurs, generating a stoichiometric and toxic byproduct.[3a,b] Bromination and elimination sequences also have been employed but use strong oxidants and produce undesirable halogen waste.[11] While these processes have been useful for the two-step introduction of alkenes conjugated to amides, these methodologies do not generally tolerate nucleophilic and reactive functional groups (e.g., alcohols and amines).[12]

Herein we report a novel lithium anilide, lithium cyclohexyl-(2,6-diisopropylanilide), LiCyan, that allows for the direct palladium-catalyzed α,β-dehydrogenation of amide substrates (Figure 1b). Furthermore, we demonstrate a generalized method for carbonyl-selective dehydrogenation of substrates with reactive heteroatom nucleophiles, including alcohols and amines (Figure 1c). These advancements eliminate the need to include inefficient protection and deprotection strategies in synthetic design where dehydrogenation of amide substrates is planned, a process that typically requires a four-step sequence.

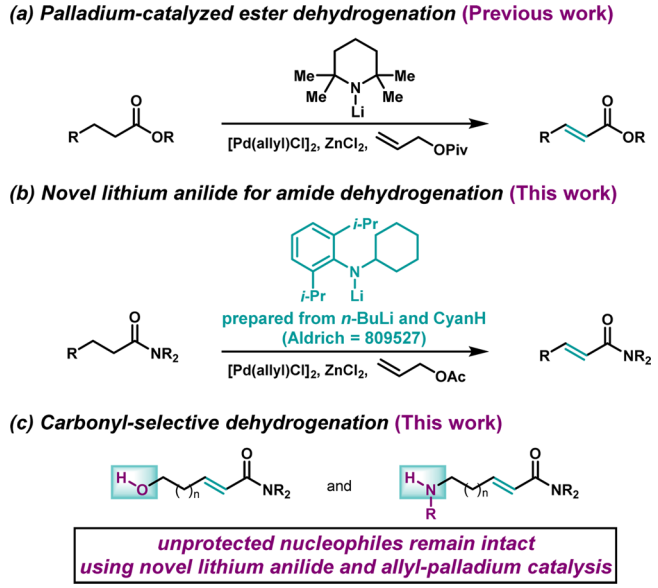

Figure 1. (a) LiTMP is an efficient base for ester and nitrile dehydrogenation, but ineffective for amide dehydrogenation. (b) Recently commercialized CyanH allows for facile amide dehydrogenation using allyl acetate as a stoichiometric oxidant. (c) Amides are selectively dehydrogenated in the presence of unprotected heteroatom nucleophiles.

Attempts to apply our previously developed oxidation system for the α,β-dehydrogenation of esters and nitriles to amides were unsuccessful and are summarized in Figure 2. The previously disclosed reaction conditions generate a zinc enolate by sequential addition of LiTMP (lithium 2,2,6,6-tetramethylpiperidine) and $ZnCl_2$, followed by oxidation with π-allyl-palladium chloride dimer and allyl acetate:[4] for the model amide substrate **1a**, use of previously described LiTMP (**3a**) resulted in a yield of only 26% with 53% conversion of the starting material. Attempts to improve these results through modification of standard reaction variables (oxidant, equivalents, temperature, time, etc.) were unsuccessful. Reasoning that the lithium amide base may play a role in determining the coordination sphere of the allyl-palladium reactive species and may impact the observed efficiency, we examined alternative lithium amide bases.

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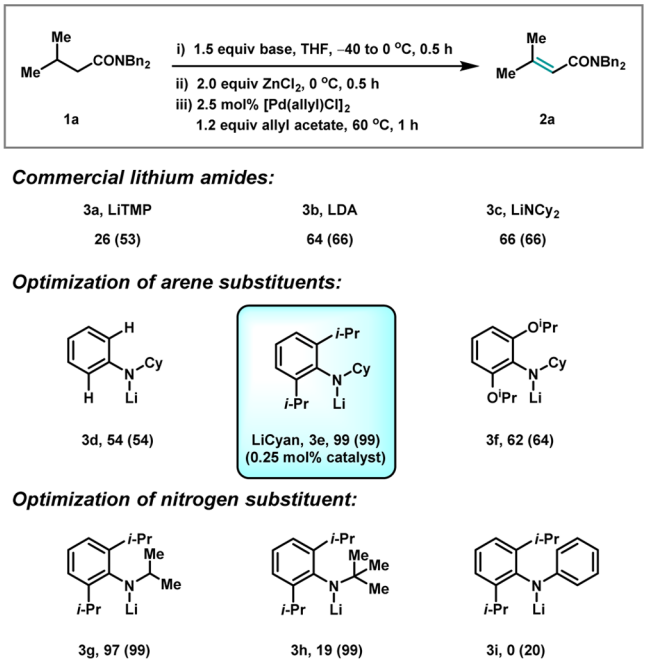
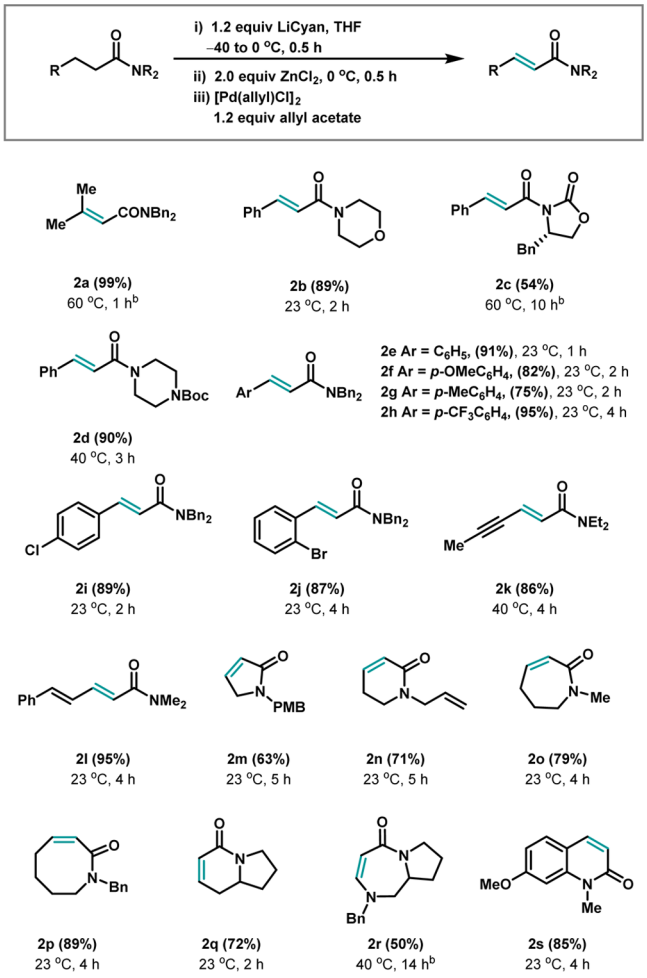


Figure 2. LiCyan is optimal for dehydrogenation. Yield was determined by ^{1}H NMR using 1,3,5-trimethyoxybenene as an internal standard. The conversion of **1a** is in parentheses.

Varying the structure of the lithium amide base in the employment of alternative commercial lithium amide bases, LDA (**3b**, 64%) and $LiNCy_2$ (**3c**, 66%), was also unsuccessful. Additional optimization focused on introduction of an arene into the lithium amide in order to provide an additional means to make structural modifications: unfortunately, only 54% of the desired oxidized product was obtained using lithium *N*-cyclohexyl anilide (**3d**). However, introduction of 2,6-diisopropyl groups on the aryl ring, LiCyan (**3e**), resulted in complete conversion and a ^{1}H-NMR yield of 99%. Exchange of the isopropyl groups for isopropoxy groups by using lithium *N*-cyclohexyl 2,6-diisopropoxyanilide (**3f**) resulted in a decreased yield of 62%. Optimization of the alkyl fragment established that the yield increased in the order Ph < *t*-Bu ≪ *i*-Pr ≈ Cy.[13] When the catalyst loading was reduced by an order of magnitude to 0.25 mol percent with LiCyan as base, a yield of 99% was still obtained.[14] CyanH is readily synthesized on preparative scale via reductive amination and recrystallization. Additionally, it is routinely recovered from dehydrogenation reaction mixtures in yields up to 99%.

After efficient conditions for amide α,β-dehydrogenation were determined, we investigated the scope of this transformation (Scheme 1). It was found that a number of different amides were tolerated in addition to the dibenzyl amide functionality in **2a**, which on a 10 mmol scale was produced in 99% yield. This methodology can access a morpholine amide (**2b**), which could be converted to an enone using an organometallic nucleophile.[15] Activated substrates, such as the acyl oxazolidinone **1c**, could also be dehydrogenated to provide **2c**,[16] which have been used for diastereoselective 1,4-conjugate additions.[17] While incomplete conversion was observed at room temperature, increasing the temperature to 60 °C resulted in full conversion. A Boc-protected piperazine underwent dehydrogenation to provide **2d** in 90% yield. Synthesis of conjugated systems with electron-rich and -deficient substitution at the β-position had minimal impact

Scheme 1. Amide α,β-Dehydrogenation Scope[a]



[a]Isolated yield, temperature, and time for the oxidation stage are indicated. [b]1.5 equiv of LiCyan was used.

on formation of the dehydrogenated products **2e**−**h**. Products derived from competitive oxidative addition of the aryl chloride (**2i**) and aryl bromide (**2j**) functionality were not observed under the optimized reaction conditions. Formation of enyne (**2k**) and diene (**2l**), which could be useful as substrates for alternative modes of reactivity, proceeded in excellent yield, 86% and 95%, respectively. A brief investigation of lactam substrates revealed that normal- and medium-sized rings (5−8 membered rings) with alkyl, allyl, and benzyl functional groups at nitrogen were viable substrates for α,β-dehydrogenation (**2m**−**2q**). An amino group at the β-position of the amide did not prevent formation of the product **2r**. It has previously been shown that amide α,β-dehydrogenation with DDQ is facile when aromaticity is a driving force;[18] likewise, our optimized conditions can provide such substrates in good yield (e.g., **2s**). Overoxidation of compounds that can become aromatic (e.g., **2n** and **2q**) was not observed under the conditions employed. Dehydrogenation of mono-β-substituted amides provided exclusively *E*-selective products.[19] Although the dehydrogenation conditions described herein are mild and allow for the selective dehydrogenation of a wide variety of amides, one limitation is that α,α-disubstituted amides are generally not viable substrates due to the difficult deprotonation of these compounds. In addition, dehydrogenation adjacent to tosyl-

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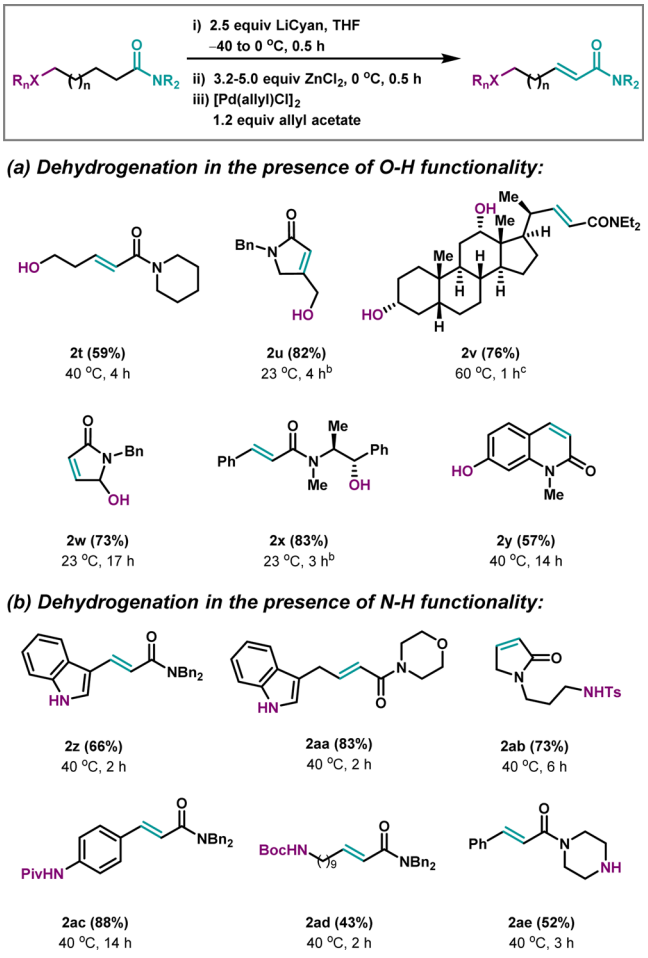
protected and carbamate-protected amides (e.g., Boc, Cbz) was not possible under the conditions employed.

With a preliminary understanding of the constraints on the scope for α,β-dehydrogenation of amides, we began to investigate substrates that contain nucleophilic heteroatoms (Scheme 2). While a multitude of synthetic technologies can oxidize or functionalize alcohols in the presence of carbonyl groups,[20] methods for the opposite mode of dehydrogenation selectivity have been elusive except for a small number of specialized substrates.[12] Such a methodology would improve the synthetic efficiency of accessing α,β-dehydrogenated carbonyl compounds by averting protection and deprotection concession steps. It was hypothesized that the optimized reaction conditions with additional anilide base would tolerate acidic and nucleophilic heteroatom functionality prone to oxidation.[21] The substrate **1t** (Scheme 2a) was subjected to the standard reaction conditions, and it was found that the primary alcohol functionality remained intact, providing the product **2t** in 59% yield. This selectivity trend was also observed for the α,β-dehydrogenation of lactams, as evidenced by the formation of **2u** in 82% yield. Secondary alcohols did not interfere with amide α,β-dehydrogention, as seen with the formation of the diol product **2v** in 76% yield and the hemiaminal substrate **2w**.

Scheme 2. Carbonyl-Selective Amide α,β-Dehydrogenation[a]



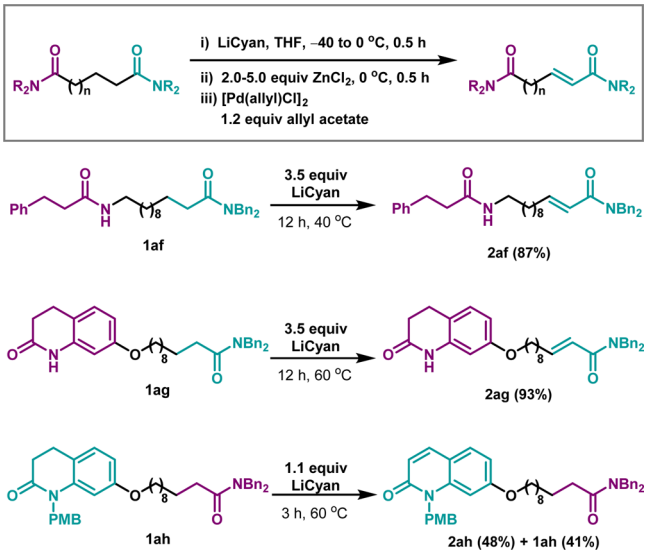
[a]Isolated yield, temperature, and time for the oxidation stage are indicated. [b]2.2 equiv of LiCyan was used. [c]3.5 equiv of LiCyan was used.

The hemiaminal substrate **2w** is notable as this functionality readily undergoes oxidation by an even wider variety of oxidants than do simple alcohols. In a similar vein, activated benzylic alcohols were not converted to phenyl ketones, but provided the α,β-unsaturated amide, as in **2x** (83%) derived from the Myers' pseudophedrin auxiliary. Akin to alcohols, phenols are also prone to oxidation, but the product **2y** could be obtained in 57% yield.

In addition to substrates that contain O–H functionality, it was found that the N–H functional group is also tolerated. Scheme 2b illustrates that unprotected indoles (**2z**–**aa**), a sulfonamide (**2ab**), an anilide (**2ac**), and a carbamate (**2ad**) are tolerated. The secondary-amine containing product **2ae** could be isolated in good yield (52%), which is surprising given amines are known to undergo oxidation catalyzed by palladium.[22] Although oxidation and the nucleophilicity of the amine functionality can be suppressed under acidic conditions by protonation,[23] this mode of reactivity is unavailable under the basic conditions of the present oxidation system.

Scheme 3 demonstrates that amide or lactam protecting group selection can determine which carbonyl in a substrate with more than one carbonyl undergoes dehydrogenation. While mono *N*-substituted amides are tolerated as spectator groups, they cannot be α,β-dehydrogenated under the reaction conditions. Substrate **2af** can be formed in an excellent 87% yield. Even a lactam that is more easily oxidized by virtue of the byproduct being aromatic does not interfere in the dehydrogenation of the *N*,*N*-disubstituted amide **2ag**. This trend can be reversed to the more typical selectivity mode[24] through the introduction of a PMB protecting group on the lactam nitrogen and by using a limited quantity of LiCyan, which results in formation of **2ah** in an isolated yield of 48% as the single dehydrogenated product in addition to 41% recovered starting material, **1ah**. These examples clarify how choice of protecting group and equivalents of base can determine the reaction outcome.

Scheme 3. Protecting-Group Controlled α,β-Dehydrogenation



Employing allyl-palladium catalysis, a method for the dehydrogenation of amides has been developed using a novel, recyclable anilide base, LiCyan. Because alcohols and amines

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are tolerated under these reaction conditions, it is not necessary to subdue these readily oxidized functionalities through tedious multiple-step protecting group sequences. Moreover, CyanH may have future use in alternative base-mediated processes or transition-metal catalyzed reactions as a hindered, monodentate anilide ligand.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/jacs.5b12924.

Experimental procedures and spectroscopic data for all new compounds including ^{1}H- and ^{13}C-NMR spectra (PDF)

■ AUTHOR INFORMATION

Corresponding Author

*timothy.newhouse@yale.edu

Notes

The authors declare no competing financial interest.

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